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Safety and Efficacy of Coronary Intravascular Lithotripsy for Calcified Coronary Arteries – A Systematic Review and Meta-Analysis

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Abstract:

Objectives: Intravascular lithotripsy (IVL) clinical efficacy and safety in the treatment of calcified coronary artery disease (CAC) is not well known. We sought to assess IVL safety and efficacy in CAC.

Methods: A comprehensive online databases search were performed to identify intravascular lithotripsy studies in patients with coronary artery disease. The primary outcome was IVL related change in the mean pre and post-procedural diameter of the coronary artery.

Results: A total of 4 studies with 282 patients were included. The mean pre-IVL coronary diameter for all patients was 1.01mm, while the mean post-IVL coronary diameter was 2.70mm. The mean pre-post IVL diameter difference of coronary arteries on the pooled analysis was significantly lower by 4.08 mm (95% CI -4.94 to -3.30, p≤0.00001). The Overall increase in the post-IVL lumen diameter was significantly higher than the pre-IVL diameter with a mean difference of -4.16 (95% CI -5.08 to -3.24, p=0.000001). However, compared to pre-IVL, there was a significant reduction in the overall mean difference of luminal calcium angle after IVL of the stented coronary arteries (0.09, 95% CI 0.002-0.16, p=0.01).

Conclusion: Intravascular lithotripsy can offer a significant improvement in the vessel lumen to facilitate coronary stent delivery and deployments in severely calcified coronary arteries.

Keywords: lithotripsy; Intravascular lithotripsy; Shockwave Intravascular Lithotripsy; Coronary artery calcification; Left coronary circulation

Article highlights:

- Intravascular lithotripsy can yield significant lumen gain of up to 4.16mm by disrupting the calcium in the media and intima coronary arteries.
- IVL has the best yield in severe CAC with stenosis >50%, and calcium angle >270 degrees as seen on intravascular imaging, facilitating stent delivery and preventing coronary recoil.
- Intra-coronary imaging helps characterize and evaluate coronary calcification and guide IVL therapy in patients with severely calcified lesions.

1. **Introduction:**

About 20% of the patients undergoing Percutaneous Coronary Intervention (PCI) have treatment failure secondary to severe coronary artery calcification (CAC). CAC is an independent factor that reduces the likelihood of successful PCI by expanding drug-eluting stents (DES) [1, 2].

Several techniques are frequently employed to facilitate calcium fracture in patients with CAC, including high-pressure non-compliant balloons, cutting balloons, excimer lasers, rotational and orbital atherectomy devices [3]. However, these techniques are associated with increased risk of complications or may risk stent disruption when PCI has already been performed with under expansion of stent [4]

Coronary intravascular lithotripsy (IVL) has been recently developed in order to manage CAC. The concept of IVL is similar to lithotripsy used in nephrolithiasis. IVL delivers circumferential, unfocused, and pulsatile energy to safely disrupt calcium within the target lesion. The purpose is to fracture the calcified plaque to gain enough lumen diameter to pass and deploy the DES [5] successfully.

IVL has been shown to offer better safety, given the minimal vascular approach and lower procedure-related complications. The ultrasonic waves travel through a balloon-based small size catheter disrupting only the superficial and deep calcium deposits with limited risk of vascular rupture or dissection [6].

Given the limited data in the efficacy and safety of IVL, we aimed in this systematic review to review the literature on the efficacy and safety of IVL in terms of coronary vessel dilatation.

2. Methods:

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Figure 1)

2.1 Eligibility criteria

Studies were included if they met all the following inclusion criteria: 1) studies that evaluated coronary shock wave intravascular lithotripsy, 2) studies of patients with the right and left coronary circulation calcified disease. For inclusion, the studies had to report data that evaluated the effectiveness of shockwave intravascular lithotripsy for left coronary circulation with baseline pre and post-procedural changes in vessel diameter. The studies also had to report data on shockwave intravascular lithotripsy effectiveness for left coronary circulation with baseline pre and post-procedural changes in vessel diameter.

2.2 Search strategy:

A literature search of PubMed, EMBASE, Cochrane Central, and ClinicalTrials.gov databases were searched for any available randomized clinical trial and observational studies from inception till

September 2020. The search items include medical subject headings (MeSH) and keywords: “intravascular shockwave lithotripsy,” “coronary lithotripsy,” “IVL,” “S-IVL,” “acute coronary syndrome,” “ST-elevation myocardial infarction,” “non-ST elevation myocardial infarction,” “unstable angina,” “stable angina,” “calcified coronary artery disease,” “ failed percutaneous coronary intervention,” “stent under expansion,” “drug-eluting stent,” and “failed rotational atherectomy.” These terms were combined using Boolean operators (“AND” or “OR”), and final results from all the possible combinations were downloaded into an EndNote library. Additional studies were identified by reviewing the reference lists of potentially relevant studies. The full search strategy is shown in the PRISMA diagram (Figure 1) and Supplemental file 1.

2.3 Study Selection:

All studies, including any available clinical trials or observational studies, were evaluated. Two authors (Y.S and S.B) independently reviewed the search results for studies that met the eligibility criteria. Uncertainty regarding study inclusion was resolved by consensus with a third author (W.U). The first phase of screening involved screening of titles and abstracts meeting inclusion criteria. The second phase of screening required full-text reading of articles that enable identifying items for data extraction based on the inclusion criteria. Irrelevant articles at this stage were excluded with reasons, as shown in Figure 1.

2.4 Data collection and statistical analysis

Statistical analysis was performed using the Cochrane Review Manager (RevMan) version 5.3. Data from each study that met the inclusion criteria were extracted into a table. The table's data elements included the country of the study, age of participants, sex of participants, sample size, comorbidities of participants, procedural parameters, safety, and follow-up. A random-effects model (inverse variance) was used to calculate the pooled mean difference and SD for luminal diameter change with a probability value of $p<0.05$ considered to be statistically significant. The “test for overall effect” was reported as z value corroborating the 95% confidence interval's inference. Higgins I-squared (I^2) was determined as a measure of statistical heterogeneity where values of ≤ 50% corresponded to low to moderate heterogeneity while values ≥75% indicated high heterogeneity. The publication bias was depicted graphically and numerically as a forest plot, and Egger’s Regression Equation (ERE). The quality assessment of the included articles was performed using the Cochrane guidelines for the systematic review and meta-analysis, and Newcastle–Ottawa scale (NOS) where each study was screened for five different types of bias (selection, performance, detection, attrition, and reporting bias). The NOS scale score ranged from 0-9; a score of 7 and above is considered high quality.

3 Results:

3.1 Search Results and Study Characteristics:

Our search identified 2901 articles. Following duplicate (n=147) removal and irrelevant items (n=2684), 70 articles were reviewed in full-text form. Based on the selection criteria, 4 articles qualified for final analysis consisting of two prospective, multicenter, single-arm, and interventional studies [9-12]. The detailed PRISMA flow diagram is shown in Figure 1.

A total of 282 patients from 4 studies were included in our review. The baseline demographic characteristics, comorbidities, and procedural characteristics are shown in Table 1. The mean age of the population was 70 years. The baseline comorbidities of the population are shown in table 1. A total of severely calcified lesions (n=216, 71 %) were treated with IVL, where all the population included had severe coronary artery calcification and underwent an IVL procedure. The procedural characteristics include mean value: Balloon size (4.0 x 12mm), Balloon pressure (6atm), Catheter size (6fr).

3.2 Pooled Analysis:

The pooled analysis of the included studies is shown in Figure 5. The overall mean lumen gain after IVL of severely calcified vessels was 4.08mm (95% CI -4.94 to -3.30, p≤0.00001). (Figure 2) The heterogeneity among the included studies' outcomes was significantly higher with an I^2=86% (p≤0.0001). (Figure 2A) The Disrupt CAD II study contributed more than one-third of the total population. A sensitivity analysis was performed by excluding the study by Brinton et al. and showed heterogeneity of 0%. (Figure 2B) The high heterogeneity by including Brinton et al. can be explained by under-reporting of IVL pre and post lumen area due to the absence of optical coherence tomographic view of vessels to measure lumen area.[9] However, under the random-effects model's assumption, the distributed weight to estimate the summary effect size was comparable among all four studies (22.4% to 27.8%).

The overall increase in the post-IVL lumen diameter was significantly higher than the pre-IVL diameter. The mean difference observed was -4.16 (95% CI -5.08 to -3.24, p=0.000001) (Figure 3). The heterogeneity among the outcomes of the included studies was moderate I2=70% (p=0.07). There was a significant reduction in the overall mean difference of luminal calcium angle after IVL (0.09, 95% CI 0.002-0.16, p=0.01). There was no heterogeneity recorded in the included studies (I2=0%). (Figure 6)

The overall increase in the post-IVL lumen diameter after coronary stenting was also significantly higher than the pre-IVL diameter. The mean difference observed was -2.17 (95% CI -2.70 to -1.63, p=0.000001) (Figure 3). However, compared to pre-IVL, there was a significant reduction in the overall mean difference of luminal calcium angle after IVL of the stented coronary arteries (0.09, 95% CI 0.002-0.16, p=0.01) (Figure 3). The incidence rate of complications (event/total cases x 100), including pooled

MACCE and individual components of MACCE during in-hospital, 30-days, and 6-month follow-up, is shown in figure 4. The heterogeneity among the included studies' outcomes was none to minimal I2=0%-I2=37% (p=0.36, p=0.22), respectively (Figure 3).

3.3 Quality of Included Studies:

The included studies' methodological quality was moderate based on the mean New Castle Ottawa Scale (NOS) score of 6. The retrospective nature of the study's randomization could not be achieved; this raised concern for selection bias. However, the included population was matched based on their demographic and baseline characteristics, minimizing this risk. The risk of attrition bias was reduced by adaptation of intention to treat model. Due to the index procedure's interventional nature, and the study's single-arm design, the risk of performance bias could not be determined. Similarly, an accurate assessment of the detection bias risk was limited. Although one can speculate a high risk of detection bias based on the fact that investigators and patients were unblinded, the risk was minimal, due to the objective angiographic assessment of the effect size. The risk of reporting bias was minimal due to adequate reporting of outcomes. The detailed NOS is given in Table 2. The detailed bias summary and assessment are shown in Figure 5 and Figure 6.

3.4 Publication Bias:

The plot's vertical axis used standard error to estimate the sample size of the study, plotting large population studies on top and smaller at the bottom. The horizontal spread reflected the power and effect size of the included studies. Our funnel plot was not symmetrical on visual assessment, indicating that the limited scatter might be due to publication bias. (Figure 7) The numerical assessment of publication bias was done using Egger's regression model that failed to show any publication bias or small study effects (ERE ≈ p=0.771). Furthermore, the heterogeneity among the outcomes of the included studies was self-explicable. First, as per the Cochrane handbook of the systematic review and meta-analysis, if the total count of included studies is less than ten, it is not possible to differentiate between true heterogeneity and findings merely by chance. Second, while all the studies unanimously supported the IVL, the high percentage of variability could be explained by the sampling error.

4. Discussion:

Our study is the first systematic review and meta-analysis to statistically pool the evidence for the use of IVL for the left coronary calcific disease. The pooled results of the four included studies suggest that IVL can get a luminal gain by 4.12mm with the success of implanting an eluting drug stent (DES). The overall post IVL lumen diameter was significantly higher than the pre-IVL diameter with a significant reduction in luminal calcium angle after IVL of the stented coronary arteries (0.09, 95% CI 0.002-0.16, p=0.01). IVL

is relatively safe procedure with very limited complication given in hospital MACCE (total n=11; Dissection type B=4; MI=7), 30-day MACCE (total n=16; cardiac mortality=1; MI=8; Dissection type B=4; Stent thrombosis=2, Target vessel revascularization(TVR)=1), and 6 months MACCE (total n=8; cardiac death=3; MI=5)

Left calcified coronary disease can increase complications along with stent under expansion, which increases the risk of stent thrombosis, and higher MACCE. Calcium debulking procedures have traditionally been the first-line approach for left CAC disease to either deploy DES or to revascularize the affected vessel. These techniques debulk the superficial calcium, but occasionally at the cost of causing high intimal hyperplasia leading to early restenosis and distal embolization [7, 8]. Furthermore, acute coronary syndromes, including ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI), are not likely to undergo rotational atherectomy [7]. Coronary IVL, as a contemporary intervention, bears a better safety profile and potentially similar efficacy. It uses ultrasonic waves without any burr holes to target both superficial and deep layers of calcifications. Owing to the low-pressure balloon inflation with a small guided catheter, IVL is preferred over prior calcium debulking technique due to less vascular intimal hyperplasia, limiting restenosis of a vessel and longer patency.

Our meta-analysis demonstrates that IVL independently can significantly reduce the calcium burden of the left coronary vessel. Of the included studies, DISRUPT CAD I by Brinton et al. was the first study to look at the efficacy of IVL [9]. A total of 60 patients were enrolled from seven different hospitals in five countries. The included study population had ≥1 lesion requiring PCI with heavy calcification, diameter stenosis ≥50%, and lesion length ≤32 mm. The primary outcome of the study was to assess clinical efficacy: the ability to reduce mean diameter stenosis <50% with no evidence of MACCE at 30 days follow-up. The results of DISRUPT CAD I showed a mean decrease of calcium angle, calcium thickness, lumen area was 23 º, 0.02 ± 0.01 mm, and 4.23 ± 2.33 mm, respectively. The calcium fracture was achieved in >25% of the lesions with a mean acute diameter gain of 2.1mm. The study resulted in favorable outcomes to deploy stents in up to 95% of patients who underwent IVL. Ali et al. performed a subgroup analysis of the DISRUPT CAD I to study plaque properties and complications of IVL using optical coherence tomography (OCT). Ali et al. included 31 patients in subgroup analysis that underwent IVL and resulted that calcium fracture was highest in heavily calcified lesions (highest vs. lowest percentile of calcium: 77.8 % vs. 22.2 %, p=0.057). The mean acute luminal after IVL was 2.1 $mm^{2,}$ which can be expanded to 5.94 ± 1.98 mm^2 with DES. The mean stent expansion was 112.0 ± 37.2%. Deep

dissection, as part of the IVL procedure, was seen in 13% of the cases. The included population had no incidence of vessel perforation, slow flow/no reflow, and closure after IVL procedure [10].

Recently, a large prospective study, DISRUPT CAD II by the same authors (ALI et al. [11]), assessed the efficacy of IVL in severely calcified lesions. The primary outcome of the study was MACCE (target vessel revascularization, myocardial infarction, and cardiac mortality) after IVL. This study reported a mean drop in calcium angle, calcium thickness, lumen area by 51º, 0.04 ±0.2 mm, and 4.83 ± 3.04mm, respectively. The post IVL acute luminal gain was 0.83 ± 0.47mm that increased to 7.7 ± 7.1% by DES implantation with residual stenosis of 32.7± 10.4%. IVL associated MACCE developed in 7 (5.8%) patients with non-Q wave myocardial infarction. The assessment of the rest of the complication review at 30 days follow up showed no perforation, dissection, or early in-stent stenosis. The most recent study performed by Aksoy et al. in 2019 reported better results with IVL. He reported an improvement in stenosis from a baseline of 71.8±13.1% to 45.1 ±17.4% after IVL and 17.5±15.2% after stenting [12]. Luminal diameter improvement from 1.01±0.49mm to 1.90±0.61 with IVL and 2.88±0.56 mm after stenting. An 84.6% success rate has been reported in patients who had IVL as their primary procedure. Another study named IntravaScular lithotripsy for the Management of undILatable coronary stEnt: (SMILE) by Lelasi et al.[13] published in May 2020, access the safety of IVL in a calcified disease that present as in-stent restenosis, the study reported that IVL was a success in 87.1% of cases with significant improvement in minimal stent diameter (pre IVL 0.81 mm; post IVL 3.23 mm; p=0.00001) and minimal stent cross-sectional area (pre IVL 3.35mm; post-IVL 7.61mm; p=0.00001). The study also reported only 1 case of non-fatal STEMI that occurred during periprocedural timing due to IVL balloon rupture, and there was no case of TVR, cardiac mortality, and stent thrombosis. In addition, Similarly, Wong et al., in his case series of 3 patients, reported reasonable success rates without any complications [14]. In terms of complications, MACCE reported in most studies is a combination of cardiac death, TVR, MI, and coronary artery dissection. The complications of IVL are most commonly due to balloon inflation of balloon rupture. We found MI as the most common complication after IVL at in-hospital, 30 days and six months follow up. The coronary artery dissection type B is the second most common complication after IVL.

The major limitation of all studies was a small sample size and non-randomized control groups. Our meta-analysis pooled all studies to get a slightly larger sample size in order to see the more substantial evidence in favor of IVL. The 30-day and 6-month outcomes from available data show the capacity of lithoplasty to successfully improve the expansion of the vessel to deploy stent with minimal vessel wall

injury and lower MACCE. Our study also highlights the paucity of clinical studies and the need for further controlled studies on longer follow-up duration.

Recently initiated trials around the efficacy of IVL include DISRUPT CAD III (NCT03595176): a multicenter prospective study to evaluate the safety and effectiveness of the IVL procedure. In this study, approximately 392 subjects will be enrolled at 50 different sites. A minimum of half of the study population will be enrolled in the United States. A follow-up will be at discharge, 30 days, 6, 12, and 24 months. DISRUPT CAD IV (NCT04151628): is a prospective single-arm study that would enroll 72 patients from Japan. Subjects will be followed at discharge, 30 days, 6,12, and 24 months. Another ongoing study, RAINBOW (NCT04013906) trial, a randomized clinical trial to evaluate the plaque modification after rotational atherectomy vs. IVL before DES implantation.

6. Limitations:

Due to the sparse data, only observational studies were involved; more studies, including randomized, double-blind studies, should be performed in the future to review the efficacy and to compare the complications of IVL. The included studies were single-arm with no comparison to other calcium debulking techniques, including atherectomy. We didn't include SMILE registry results in our study given the data available in medians and no availability of standard deviation. Although IVL appears to be associated with a low incidence of overall complications based on our present findings, further evidence from RCTs and longer-term follow-up is required to advocate its routine use in patients with CAC.

7. Conclusion:

Intravascular lithotripsy can offer a significant improvement in the vessel lumen to facilitate coronary stent delivery and deployments in severely calcified coronary arteries. Further evidence from RCTs and longer-term follow-up are required to advocate its routine use in patients with CAC.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

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Table 2: The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyze

Figure 1: PRISMA Flow of the search strategy for systematic review and meta-analysis

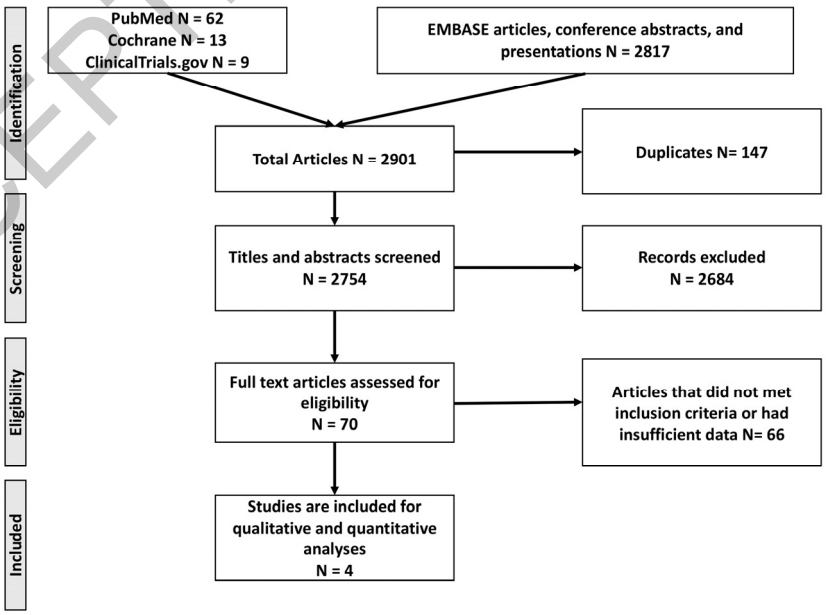
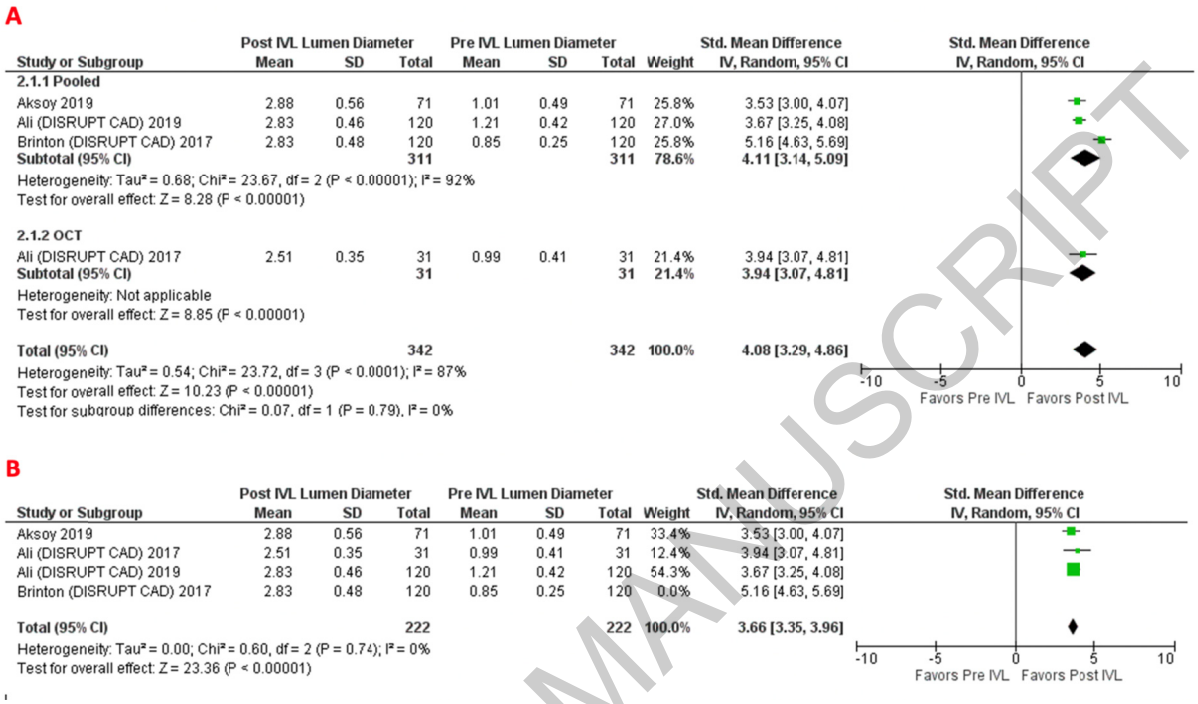


Figure 2: A) Forest plot showing a random effect model with mean differences for pre- and post-intravascular lithotripsy results. B) Sensitivity analysis of pre- and post- intravascular lithotripsy lumen diameter.



Abbreviations: IVL: Intravascular Lithotripsy

Figure 3: Forest plot showing pre and post IVL outcome of minimal lumen area circumference, minimal lumen area calcium angle, minimal stent area, and minimal stent area calcium angle.

Abbreviations: MLA C: Minimal Lumen area circumference; MLA CA: Minimal Lumen Area Calcium Angle; MSA: Minimal Stent Area; MSA CA: Minimal Stent Area Calcium Angle; IVL: Intravascular Lithotripsy

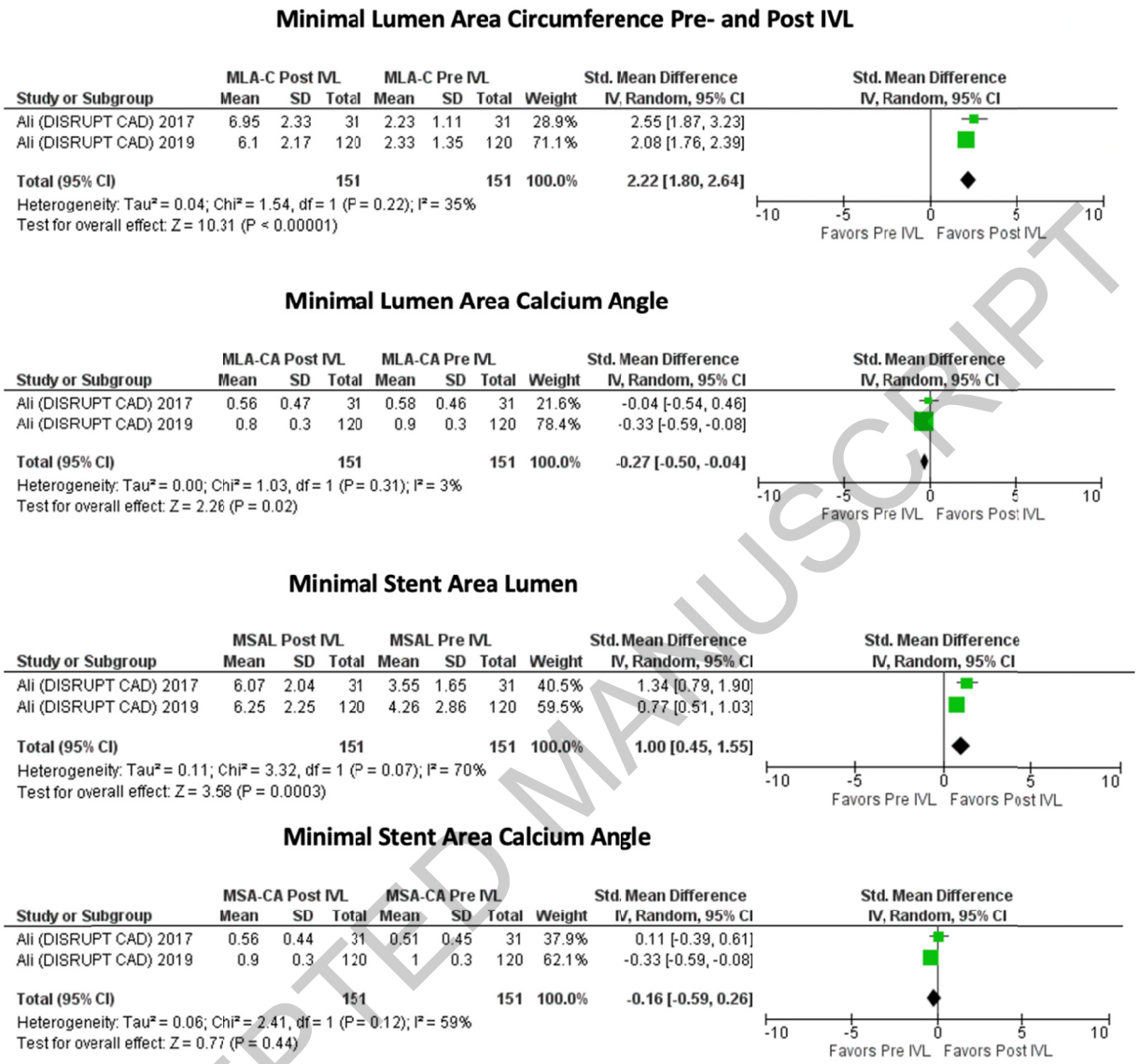


Figure 4: Bar chart showing the incidence rate of Major Adverse Cardiac and Cerebrovascular Events after IVL (MACCE), and its components based on durations.

Abbreviations: CD: Cardiac Death; DS: Coronary Dissection Type-B; MI: Myocardial Infarction; ST: Stent Thrombosis; TVR: Target Vessel Revascularization; IH: In Hospital; 30D: 30 Days; 6M: 6 Months

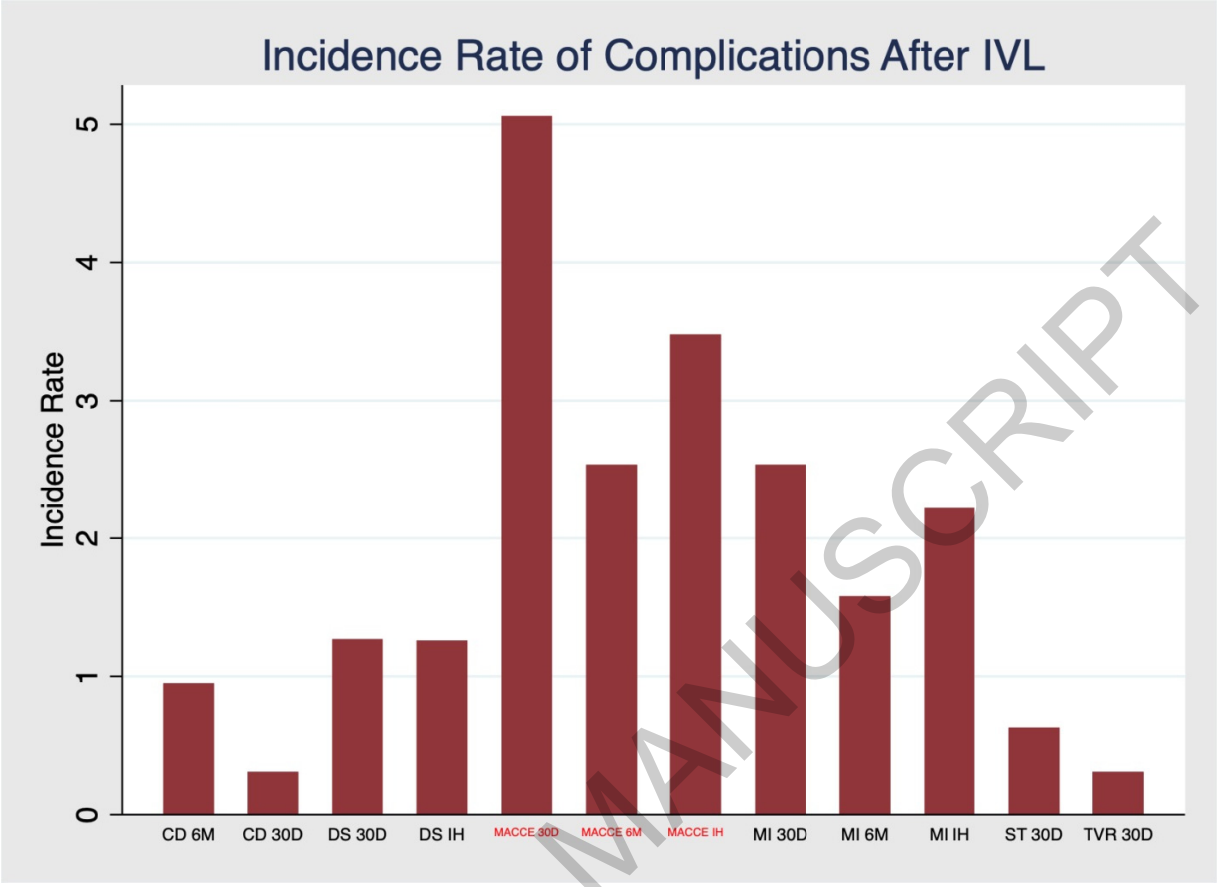


Figure 5: Summary of bias assessment of included studies.

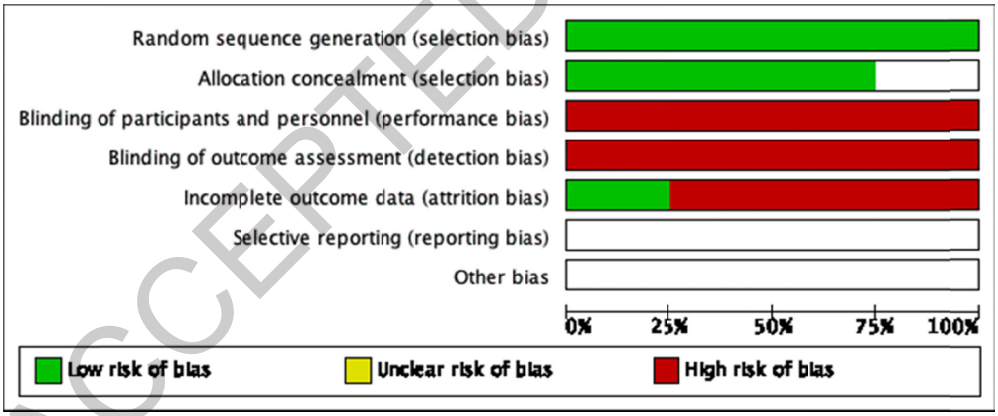


Figure 6: Bias assessment of included studies

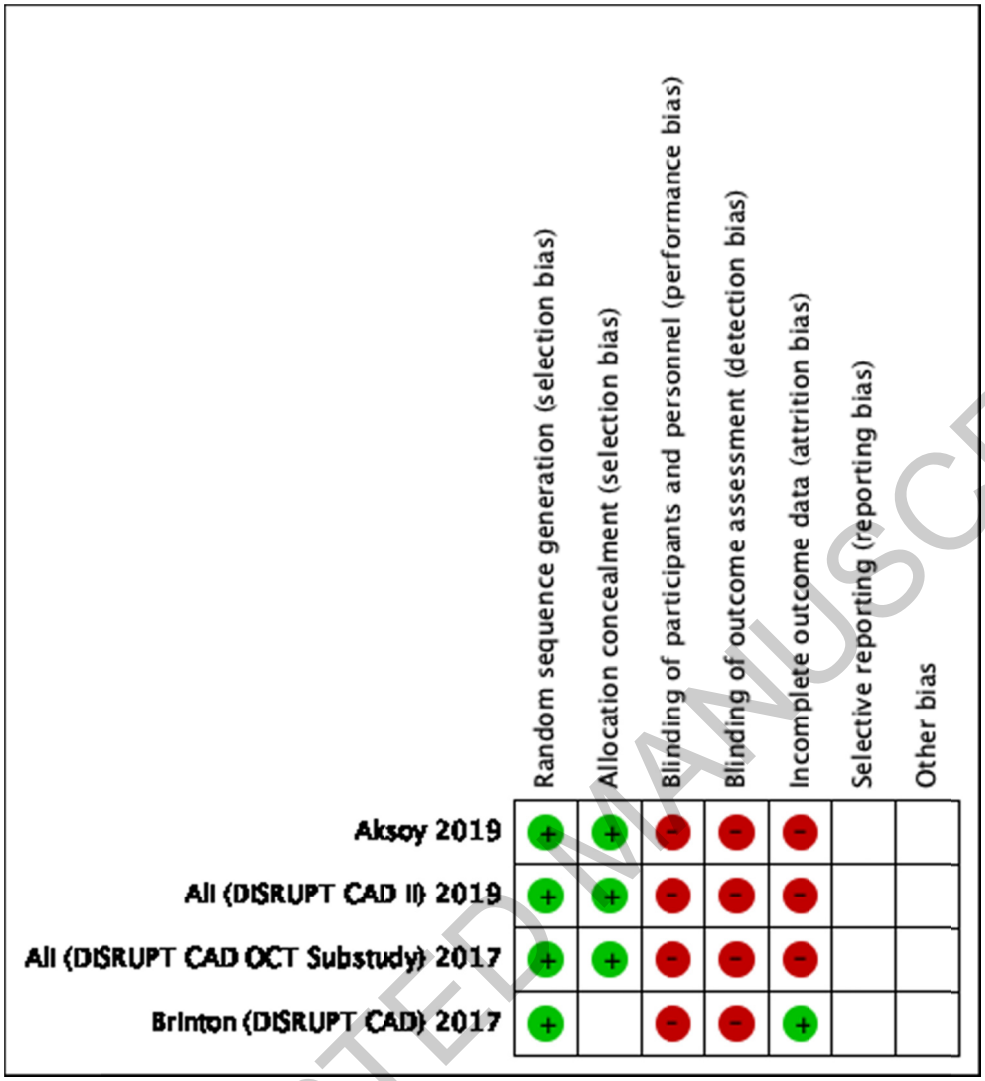


Figure 7: Funnel plot showing publication bias.

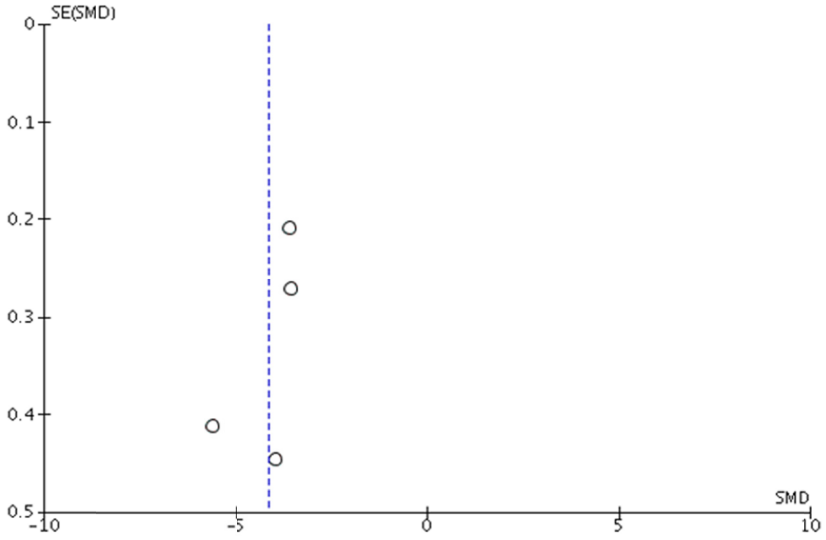


Table 1. Baseline demographics, comorbidities, and procedural characteristics of study population.

Author	**DISRUPT CAD I Brinton et al. – 2017** [9]	**DISRUPT CAD OCT sub-group study Ali ZA – 2017** [10]	**DISRUPT CAD II Ali et al. – 2019** [11]	**Aksoy et al. – 2019** [12]
Country	Multi-national (5 countries)	Multi-national	Multi-national	Germany
Age (Years)	73 ± 7	71 ± 10	72 ± 10	76 ± 10
Male % (n)	80 (48)	80 (25)	78 (94)	51 (72)
Sample Size (n)	60	31	120	71
ACS % (n)	40 (24)	42 (13)	26 (31)	45 (32)
HTN % (n)	80 (48)	24 (77)	80 (96)	93 (66)
DM % (n)	30 (18)	7 (23)	32 (38)	34 (24)
Dyslipidemia % (n)	80 (48)	26 (83)	72 (86)	62 (45)
Smoking % (n)	15 (9)	7 (23)	13 (16)	37 (26)
TIA/Stroke	13 (8)	-	3 (4)	17 (12)
Prior coronary intervention % (n)	23 (14) - CABG	-	7 (8) CABG	3 (4)
Stenosis > 50%, (n)	60	-	120	-
# of cycles of S-IVL	-	-	10	-
Balloon size (mm)	4.0 x 12	4.0 x 12	4.0 x 12	4.0 x 12
Pressure atm (pre-IVL / post-IVL)	4 atm / 6 atm	6 atm	4 atm / 6 atm	4 atm / 6 atm
Catheter Size (French Fr)	6 F	6 F	6 F	6F (18% 7F)

Table 2. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis

	Selection					Outcome			
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Comparability of the cohort	Assessment of outcome	Enough follow-up duration	Adequate follow-up	Total score
Brinton (DISRUPT CAD) 2017 [9]	*	N/A	*	*	N/A	*	*	*	6

No. of stent pass	100% (60)	100% (31)	100% (120)	-
Approach	-	Transradial or Transfemoral	-	-
Left main Stem Blockage % (n)	2 (1)	0	0.8 (n=1)	17 (13)
LAD Blockage	47 (28)	14 (45)	63 (75)	44 (34)
LCX Blockage	13 (8)	5 (16)	12 (14)	-
Diagonal branch (DI) blockage	-	0	25.0 (30)	-
Follow up	6 months	1d	30 days	30 days

Ali (Disrupt CAD OCT) 2017 [10]	*	*	*	*	N/A	*	*	*	6
Ali (Disrupt CAD-II) 2019 [11]	*	*	*	*	N/A	*	*	*	6
Aksoy 2019 [12]	*	N/A	*	*	N/A	*	*	*	6

Footnote: Each asterisk represents one star in the Newcastle-Ottawa Scaling System (NOS). The maximum stars are 2 for comparability and 1 are for all other categories. Each star counts towards the total score. Score of 5 to 6 considered as moderate quality and 7 to 9 as high quality.

Supplementary file 1

Search Strategy

MeSH +Keyword:
Intravascular shockwave lithotripsy
Shockwave intravascular lithotripsy
Coronary lithotripsy
IVL
S-IVL
Acute coronary syndrome
ST-elevation myocardial infarction
Non-ST elevation myocardial infarction
Unstable angina
Stable angina
Calcified coronary artery disease
Failed percutaneous coronary intervention
Stent under expansion
Drug eluting stent
Failed rotational atherectomy

PubMed
(((((Intravascular shockwave lithotripsy) OR (Shockwave intravascular lithotripsy)) OR (coronary lithotripsy)) OR (IVL)) OR (S-IVL)) AND ((((((((((Acute coronary syndrome) OR (ST-elevation myocardial infarction)) OR (Non-ST elevation myocardial infarction)) OR (Unstable angina)) OR (Stable angina)) OR (Calcified coronary artery disease)) OR (Failed percutaneous coronary intervention)) OR (Stent under expansion)) OR (Drug eluting stent)) OR (Failed rotational atherectomy))

Embase Classic+ Embase 1947 (inception) to 2020 October 08

#	Searches	Results
1	exp lithotripsy/	14948

2	coronary lithotripsy.kw.	3
3	Intravascular shockwave lithotripsy.tw.	2
4	Intravascular lithotripsy.kw.	28
5	Shockwave lithotripsy.kw.	428
6	S-IVL.mp.	49
7	IVL.tw.	927
8	IVL.kw.	21
9	exp acute coronary syndrome/ or exp coronary artery disease/ or exp ischemic heart disease/ or exp non st segment elevation acute coronary syndrome/	854559
10	calcified coronary artery disease.mp. or coronary artery calcification/	5440
11	exp st segment elevation myocardial infarction/ or exp heart infarction/	409023
12	exp non ST segment elevation myocardial infarction/	15192
13	exp unstable angina pectoris/	24390
14	exp stable angina pectoris/	11539
15	Failed percutaneous coronary intervention.kw.	0
16	exp percutaneous coronary intervention/ or exp interventional cardiovascular procedure/ or exp transluminal coronary angioplasty/	148096
17	exp drug eluting stent/ or exp stent/ or exp sustained release preparation/ or exp drug eluting cardiovascular stent/ or exp drug eluting digestive stent/ or exp drug eluting nitinol stent/ or exp drug eluting sinus stent/ or exp drug eluting tracheobronchial stent/ or exp drug eluting ureter stent/ or exp drug eluting urethral stent/	203824
18	exp atherectomy/ or exp artery surgery/ or exp interventional cardiovascular procedure/ or exp coronary atherectomy/ or exp directional atherectomy/ or exp rotational atherectomy/	309653
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	16086
20	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1130411
21	19 and 20	2817

Cochrane Central Database: Date Run: 10/10/2020 00:26:53

#	Searches	Results

1	Intravascular shockwave lithotripsy	6
2	Shockwave intravascular lithotripsy	6
3	Coronary lithotripsy	14
4	IVL	39
5	S IVL	14
6	Intravasc* Lithotri*	11
7	Acute coronary syndrome	6791
8	ST-elevation myocardial infarction	3121
9	Non-ST elevation myocardial infarction	1616
10	Unstable angina	4286
11	Calcified coronary artery disease	198
12	percutaneous coronary intervention	10,644
13	Stent under expansion	48
14	Drug eluting stent	3941
15	atherectomy	462
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6	53
17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	21449
18	#16 AND #17	13

ClinicalTrials.gov search map:

Terms	**Search Results***	**Entire Database****
Synonyms		
lithotripsy	9 studies	180 studies
Litholapaxies	--	1 studies
calcified coronary artery disease	--	1 studies
coronary artery disease	9 studies	7,797 studies
Coronary Disease	9 studies	4,689 studies
myocardial ischaemia	9 studies	7,488 studies
Atherosclerosis of coronary artery	--	4 studies
Atherosclerosis of native coronary artery	--	1 studies
Atherosclerotic heart disease	--	16 studies

Terms	Search Results*	Entire Database**
Synonyms		
cardiac ischaemia	--	28 studies
Coronary Arterioscleroses	--	149 studies
coronary artery atherosclerosis	--	3 studies
coronary atheroma	--	7 studies
Coronary Atheroscleroses	--	136 studies
coronary heart disease	--	705 studies
Disease coronary artery	--	1 studies
ischaemic heart disease	--	433 studies
artery disease	9 studies	6,245 studies
arterial diseases	--	1,640 studies
arterial vascular disease	--	3 studies
Arteriopathic disease	--	1 studies
Arteriopathy	--	19 studies
artery disorders	--	1 studies
coronary artery	9 studies	5,037 studies
disease	9 studies	257,226 studies
condition	--	11,993 studies
Disorders	--	92,462 studies
artery	9 studies	11,114 studies
Arterial	8 studies	9,016 studies
Arteria	--	7 studies
coronary	9 studies	24,863 studies
Heart	9 studies	21,313 studies
Cardiac	--	9,787 studies
calcified	9 studies	325 studies
Calcification	2 studies	235 studies
calcific	--	58 studies

Terms	Search Results*	Entire Database**
Synonyms		
calcify	--	1 studies
calcifying	--	4 studies

-- No studies found

* Number of studies in the search results containing the term or synonym

** Number of studies in the entire database containing the term or synonym

ClinicalTrials.gov search results:

ClinicalTrials.gov Search Results 10/09/2020

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Disrupt CAD III With the Shockwave Coronary IVL System	Active, not recruiting	No Results Available	•Coronary Artery Disease •Myocardial Infarction	•Device: Lithotripsy	•Honor Health, Scottsdale, Arizona, United States •Scripps Clinic, La Jolla, California, United States •University of California, San Diego (UCSD) - Medical Center, La Jolla, California, United States •St. Joseph Hospital, Orange, California, United States •VA Palo Alto Health Care System, Palo Alto, California, United States •Yale New Haven Hospital, New Haven, Connecticut, United States •MedStar Washington Hospital Center, Washington, District of Columbia, United States •Emory University Hospital Midtown, Atlanta, Georgia, United States •Piedmont Heart Institute, Atlanta, Georgia, United States •Northwestern University, Chicago, Illinois, United States •and 38 more
2	Disrupt CAD IV With the Shockwave Coronary IVL System	Active, not recruiting	No Results Available	•Coronary Artery Disease •Myocardial Infarction	•Device: Lithotripsy	•Tenjinkai Shin-Koga Hospital, Kurume, Fukuoka-Ken, Japan •Sapporo Higashi Tokushukai Hospital, Sapporo, Hokkaido, Japan •Sakurakai Takahashi Hospital, Kobe, Hyogo-Ken, Japan •Higashi-Takarazuka Satoh Hospital, Takarazuka, Hyogo-Ken, Japan •Johas Kanto Rosai Hospital, Kawasaki, Kanagawa-Ken, Japan •Shonan-Kamakura General Hospital, Kanakura, Kanagawa, Japan •Kyoto-Kasura Hospital, Kyoto-shi, Kyoto-Fu, Japan •Miyazaki Medical Association Hospital, Miyazaki, Miyazaki-Ken, Japan
3	Atherectomy vs Intravascular Lithotripsy	Not yet recruiting	No Results Available	•Coronary Artery Disease	•Diagnostic Test: Rotational atherectomy	
4	ROtational Atherectomy, Lithotripsy or LasER for the Treatment of CAlcified STEnosis	Not yet recruiting	No Results Available	•Coronary Artery Disease	•Device: Percutaneous coronary Intervention	
5	Balloon Lithoplasty for Preparation of Severely Calcified Coronary Lesions	Recruiting	No Results Available	•Percutaneous Coronary Intervention •Coronary Artery Calcification •Coronary Artery Disease	•Device: Lithoplasty •Device: Conventional	•Gentofte University Hospital, Gentofte, Copenhagen, Denmark •Aalborg University Hospital, Aalborg, Denmark •Aarhus University Hospital Skejby, Aarhus, Denmark •Rigshosptalet, Copenhagen, Denmark •Odense University Hospital, Odense, Denmark •Zealand University Hospital, Roskilde Sygehus, Roskilde, Denmark

	Title	Status	Study Results	Conditions	Interventions	Locations
6	Intravascular Balloon Lithotripsy in Left Main Stem Percutaneous Coronary Intervention	Not yet recruiting	No Results Available	•Coronary Artery Calcification •Left Main Coronary Artery Disease	•Device: Left main stenting with intravascular lithotripsy	•Belfast Health & Social Care Trust, Belfast, Northern Ireland, United Kingdom •Golden Jubilee Hospital, Clydebank, Scotland, United Kingdom •University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom •King's College Hospital NHS Foundation Trust, London, United Kingdom •Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom •St George's University Hospitals NHS Foundation Trust, London, United Kingdom
7	Registry of Coronary Lithotripsy in Spain.	Recruiting	No Results Available	•Cardiovascular Diseases •Arteriosclerosis •Arterial Occlusive Diseases •Vascular Diseases •Coronary Artery Disease	•Other: Intracoronary lithotripsy (ICL)	•Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain •Hospital Clinico Universitario de Santiago de Compostela, Santiago De Compostela, Coruña, Spain •Hospital Universitario Alvaro Cunqueiro, Vigo, Pontevedra, Spain •Hospital de León, León, Spain •Hospital Universitario Lucus Agusti, Lugo, Spain •Hospital La Luz, Madrid, Spain •Hospital Central de La Defensa, Madrid, Spain
8	Shockwave Coronary Rx Lithoplasty® Study (Disrupt CAD I)	Completed	Has Results	•Coronary Artery Disease	•Device: Shockwave Coronary Rx Lithoplasty® System	•Monash Heart, Monash Health, Clayton, Victoria, Australia •St. Vincent's Hospital, Melbourne, Victoria, Australia •Clinic Pasteur, Toulouse, France •Thoraxcenter, Erasmus MC, Rotterdam, Netherlands •Skane University Hospital- Lund, Lund, Sweden •King's College Hospital, London, United Kingdom •Royal Brompton Hospital, London, United Kingdom
9	Shockwave Coronary Lithoplasty Study	Completed	No Results Available	•Coronary Stenosis	•Device: Shockwave Coronary Lithoplasty System	•St. Vincent's Hospital Melbourne, Melbourne, Victoria, Australia